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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
JEFFREY R. DAHLEN, KENNETH F. BUECHLER, and GUNARS E. VALKIRS

Appeal 2008-1230[1]
Application 09/835,298
Technology Center 1600

Decided: January 27, 2009

Before TONI R. SCHEINER, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

SCHEINER, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for assigning a prognosis to a patient with an acute coronary syndrome. The Examiner has rejected the claims as obvious over the prior art. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

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[1] Heard September 9, 2008.

STATEMENT OF THE CASE

Claim 23 is representative of the claimed subject matter:

23. A method for predicting cardiac mortality rate in a patient with an acute coronary syndrome, comprising:

drawing a sample of a body fluid from said patient,

contacting said sample with a first antibody that specifically binds to a first marker selected from the group consisting of cardiac Troponin-T and cardiac Troponin-I;

contacting said sample with a second antibody that specifically binds to a second marker selected from the group consisting of BNP, NT-proBNP, and pro-BNP;

providing means for determining binding between each of said respective markers and each of said respective antibodies,

whereby said binding provides a means for determining cardiac mortality rate.

The Examiner relies on the following evidence:

Jackowski	U.S. 5,290,678	Mar. 1, 1994

Elliott M. Antman et al., *Cardiac-Specific Troponin I Levels to Predict the Risk of Mortality in Patients with Acute Coronary Syndromes*, 335 THE NEW ENGLAND JOURNAL OF MEDICINE 1342-1349 (1996).

A.M. Richards et al., *Neuroendocrine Prediction of Left Ventricular Function and Heart Failure after Acute Myocardial Infarction*, 81 HEART 114-120 (1999).

Appellants rely, in part, on the following additional evidence:

Marc S. Sabatine et al., *Multimarker Approach to Risk Stratification in Non-ST Elevation Acute Coronary Syndromes*, 105 CIRCULATION 1760-63 (2002).

Marc A. Silver et al., BNP Consensus Panel 2004: *A Clinical Approach for the Diagnostic, Prognostic, Screening, Treatment Monitoring, and Therapeutic Roles of Natriuretic Peptides in Cardiovascular Diseases*,

10(5 Supp. 3) CONGESTIVE HEART FAILURE 1-30 (2004).

Claims 23-28, 32-34, and 38[2] stand rejected under 35 U.S.C. § 103(a) as unpatentable over Jackowski, in view of Antman and Richards.

ISSUE ON APPEAL

The Examiner concluded that it would have been obvious for one skilled in the art to establish the prognosis of a patient with an acute coronary syndrome (ACS) by measuring cardiac troponin I and BNP, both of which were known in the art as "powerful predictor[s] of death" (Ans. 7-8), because multimarker approaches to diagnosis and/or prognosis were conventional in the art, and "detecting both troponin I and BNP [would] provide the advantage of a better prediction of likelihood of death as these cardiac markers are disclosed as being detectable at different times" (*id.* at 8).

Appellants acknowledge that "the individual use of cardiac troponin and BNP for prognosis in myocardial infarction" is disclosed in the art, but contend that nothing in the art "indicates that cardiac troponins and BNP are independent of one another, or that they should be used together for purposes of prognosis in ACS" (App. Br. 12). Appellants contend that even if measuring both troponin I and BNP would have been prima facie obvious, evidence of secondary considerations "demonstrates that the claimed invention is, in fact, non-obvious" (*id.*).

The issue raised by this appeal is whether the Examiner has established, by a preponderance of the evidence, that it would have been

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[2] Claims 29-31 and 35-37 have been withdrawn from consideration.

obvious to measure both cardiac troponin I and BNP to determine the prognosis of a patient with an acute coronary syndrome.

FINDINGS OF FACT

FF1 The claims on appeal are directed to a method of determining the cardiac mortality rate and/or prognosis of a patient with an acute coronary syndrome, by determining antibody binding to two different markers in a sample of body fluid from the patient. One of the markers is the B-type natriuretic peptide (BNP), or one of its precursors (NT-proBNP or pro-BNP); the other marker is cardiac troponin-T or cardiac troponin-I.

FF2 According to the Specification,

> The term "acute coronary syndromes" ("ACS") has been applied to a group of coronary disorders that result from ischemic insult to the heart. Patients with ACS form a heterogeneous group, with differences in pathophysiology, clinical presentation, and risk for adverse events. Such patients present to the physician with conditions that span a continuum that includes unstable angina, non-ST-elevation non-Q wave myocardial infarction ("NST"-"MI"), ST-elevation non-Q wave MI, and transmural (Q-wave) MI.

(Spec. 1.)

FF3 The Specification states that "the level of BNP in a patient sample, alone or in combination with one or more additional prognostic markers, can provide prognostic information useful for predicting near-term morbidity and/or mortality across the entire spectrum of acute coronary syndromes" (Spec. 3).

FF4 Further according to the Specification,

> When stratification was performed based on the concentration of cTnI [cardiac troponin-I] at the time of

> enrollment, increasing BNP concentration remained associated with higher 10-month mortality, both among those with a cTnI ≤ 0.1 ng/mL (n=882; p=0.01) and those with a cTnI > 0.1 ng/mL (n=1630; p<0.0001) . . . After adjustment for other independent predictors of long-term mortality, including ST deviation and cTnI, increasing concentration of BNP remained associated with a higher rate of death by 10 months . . .

(Spec. 22-23).

FF5 Antman et al., cited by both Appellants and the Examiner, compared the prognostic value of measuring serum levels of creatine kinase-MB (CK-MB) and troponin I in patients presenting with unstable angina or non-Q-wave myocardial infarction (Antman et al. 1342, 1344). According to Antman et al., troponin I is a more specific and sensitive marker of cardiac necrosis than CK-MB (*id.* at 1342), and detection of cardiac troponin I in blood "is an independent risk factor that identifies patients presenting with unstable angina or non-Q-wave myocardial infarction who are at increased risk of death" (*id.* at 1347).

FF6 Richards et al., cited by both Appellants and the Examiner, determined the relationships of plasma levels of BNP, atrial natriuretic factor (ANF), N-terminal ANF (N-ANF), cyclic guanosine monophosphate (cGMP), and plasma catecholamines to left ventricular function and to prognosis in patients with acute myocardial infarction (Richards et al. 114, col. 1), and concluded that

> BNP had the highest sensitivity, specificity, positive predictive value, and negative predictive value . . . for heart failure during follow up. Multivariate analyses indicated that any one of BNP, ANF, N-ANF, or cGMP added additional information beyond clinical features, noradrenaline concentrations, and LVEF [left ventricular ejection fraction] in

> predicting heart failure or the composite end point of death and/or heart failure. Among the cardiac peptides, BNP and ANF were the most powerful in this regard, with nothing to be gained from measuring more than one of these, or N-ANF or cGMP.

(Richards et al. 118-119.)

FF7 Sabatine et al., in a post-filing reference cited by Appellants, teach that troponin I, BNP, and high-sensitivity C-reactive protein (hs-CRP), "assess different pathophysiological mechanisms in myocardial ischemia: elevations in troponin indicate myocardial necrosis; CRP is a marker of inflammation; and BNP is elevated in response to left ventricular overload" (Sabatine et al. 1760, col. 1 (internal citations omitted)). In a multivariable model containing all three biomarkers, "TnI, CRP, and BNP each provided independent and incremental prognostic information" (*id.* at 1762, col. 1), and "[t]he 30-day risk of death increased in proportion to the number of cardiac biomarkers elevated at baseline . . . , with a near doubling of the mortality risk for each additional biomarker that was elevated" (*id.* at 1761, col. 1).

FF8 Silver et al., members of the BNP Consensus Panel of 2004, in a post-filing comprehensive review of the role of natriuretic peptides in cardiovascular disease, conclude that "in the setting of HF [heart failure], both troponin I and BNP were independent predictors of survival" and "[t]he two together gave additive prognostic risk" (Silver et al. 15, col. 1).

In the setting of acute coronary syndrome and coronary artery disease (CAD), Silver et al. conclude that "[s]ensitivity and specificity for BNP will not be adequate to diagnose ischemia because many patients with unstable

angina do not have BNP elevation and the levels detected among those with elevation are similar to those seen in other conditions" (*id.*). Silver et al. concur with studies (including Sabatine et al.'s, discussed in **FF7**) showing that cardiac troponin I, C-reactive protein, and BNP, in combination, are "independently associated with adverse cardiac events, demonstrating the unique predictive information that each of these biomarkers provides" (*id.* at 15, col. 2).

FF9 The members of the BNP Consensus Panel (Silver et al.) issued the following consensus statements:

> Several studies suggest that BNP levels are predictive of sudden cardiac death. Thus, BNP levels might help us further stratify patients who might benefit from newer therapies . . .
>
> Additional biomarkers (troponin and C-reactive protein) may provide unique, adjunctive, and independent information to a BNP measurement with regard to patient outcomes.
>
> When used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at an increased risk for clinically important cardiac events related to HF and acute coronary syndrome. Such information is likely to enhance our ability to appropriately triage higher-risk HF patients and more reliably identify low-risk HF patients who may be candidates for less intensive evaluation and therapy.

(Silver et al. 16, Consensus Statements 7.1.1-7.1.3.)

PRINICIPLES OF LAW

The Examiner's rejections must be supported by a preponderance of the evidence. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988).

"The concept of *prima facie* obviousness in *ex parte* patent examination is but a procedural mechanism to allocate in an orderly way the burdens of going forward and of persuasion as between the examiner and the applicant." *In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). "If rebuttal evidence of adequate weight is produced, the holding of *prima facie* obviousness, being but a legal inference from previously uncontradicted evidence, is dissipated. Regardless of whether the *prima facie* case could have been characterized as strong or weak, the examiner must consider all of the evidence anew." *Id.* at 1472.

ANALYSIS

The Examiner concluded, based on the teachings of Antman et al. and Richards et al., that it would have been obvious for one skilled in the art to measure both troponin I and BNP because each is a "powerful predictor of death," but the two markers are expressed and peak at different times following a cardiac event (Ans. 7-8). The Examiner's rationale is essentially that the markers provide comparable prognostic information, but measuring both markers increases the probability of detecting an elevation in at least one of the markers because they peak at different times following a cardiac event.

We conclude that the Examiner has provided evidence and a rational basis sufficient to establish that the claimed invention would have been prima facie obvious to one of ordinary skill in the art. Nevertheless, this is not the end of the matter. Appellants have presented objective evidence in rebuttal. Therefore, both Appellants' evidence and the Examiner's must be

reconsidered without regard to the prima facie case (*see Piasecki*, 745 F.2d at 1472).

The Specification teaches that measuring BNP levels provides prognostic information that is independent of cardiac troponin I levels, thus, the Specification teaches that BNP and cardiac troponin I do not provide the same basic prognostic information (**FF6**). This observation is confirmed by Sabatine et al., a post-filing reference submitted by Appellants as rebuttal evidence. Specifically, Sabatine et al. teach that troponin I, BNP, and high-sensitivity C-reactive protein (hs-CRP) each provide independent and incremental prognostic information, and "[t]he 30-day risk of death increased in proportion to the number of cardiac biomarkers elevated at baseline . . . with a near doubling of the mortality risk for each additional biomarker that was elevated" (**FF7**).

Similarly, Silver et al. teach that, rather than providing comparable, or cumulative prognostic information, measuring cardiac troponin I together with BNP provides "unique, adjunctive, and independent information to a BNP measurement with regard to patient outcomes" and "when used together in a combined strategy, BNP and cardiac troponin provide a more effective tool for identifying patients at an increased risk for clinically important cardiac events" than either alone (**FF8**, **9**).

The Examiner has not cited evidence that shows that the improved prognostic accuracy resulting from measuring both cardiac troponin I and BNP, compared to measuring either alone, would have been expected based on the prior art. Having considered the Examiner's evidence in light of Appellants' rebuttal evidence, we find that Appellants' rebuttal evidence

goes directly to the merits of the invention - the "unique," "independent," and "incremental" nature of the prognostic information provided by the particular combination of BNP and cardiac troponin I - and outweighs the evidence underlying the Examiner's prima facie case of obviousness.

CONCLUSION OF LAW

The Examiner has not established, by a preponderance of the evidence, that it would have been obvious to measure both cardiac troponin I and BNP to determine the prognosis of a patient with an acute coronary syndrome.

The rejection of claims 23-28, 32-34, and 38 under 35 U.S.C. § 103(a) as unpatentable over Jackowski, Antman, and Richards is reversed.

REVERSED

cdc

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